Lysophosphatidic Acid: Friend or Foe of the Ovarian Surface Epithelium

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Introduction

Ovarian cancer accounts for more deaths among women than any other cancer of the female reproductive system, and ranks fourth in cancer-causing deaths among women. The American Cancer Society estimates that in 2005, approximately 22,220 new cases of ovarian cancer will be diagnosed, and there will be about 16,210 deaths from ovarian cancer in the United States[1]. Over ninety percent of human ovarian adenocarcinomas arise from the single layer of ovarian surface epithelial (OSE) cells that surround the ovaries[2]. It is thought that the cyclic rounds of rupture and repair of the ovarian surface epithelium induced by ovulation, predispose these cells to neoplasia[3,4].

Lysophosphatidic acid (LPA) is a phospholipid growth factor found in serum, follicular and ascites fluid. LPA plays an integral part in repairing the wound caused by follicular rupture of the epithelial surface during ovulation by stimulating OSE cell division, resulting in rapid closure and repair of the wound. LPA initiates a signaling pathway within the cells of the ovarian surface epithelium that induces enhanced cell proliferation (Figure 1). This signaling results in the down-regulation of the growth and tumor suppressor functions of a channel-forming protein, connexin43 (Cx43), which then permits an increase in cell proliferation.

These cycles of LPA-mediated down-regulation of Cx43 function, which assist in quick repair of the ovarian surface after ovulation, may also allow abnormal, pre-cancerous OSE cells to proliferate and form tumors by escaping the tumor suppressing properties of Cx43. LPA also plays an important role in promoting the vascular network required for the growth of ovarian tumors, and it is known to increase resistance of the tumor cells to chemotherapeutic agents[5]. Clinical trials are currently ongoing to determine the effectiveness of measuring the plasma levels of LPA in the detection of ovarian cancer since ovarian cancer cells and not normal OSE cells secrete LPA, resulting in elevated plasma levels of LPA in about 90% of women with early stages ovarian cancer[6].

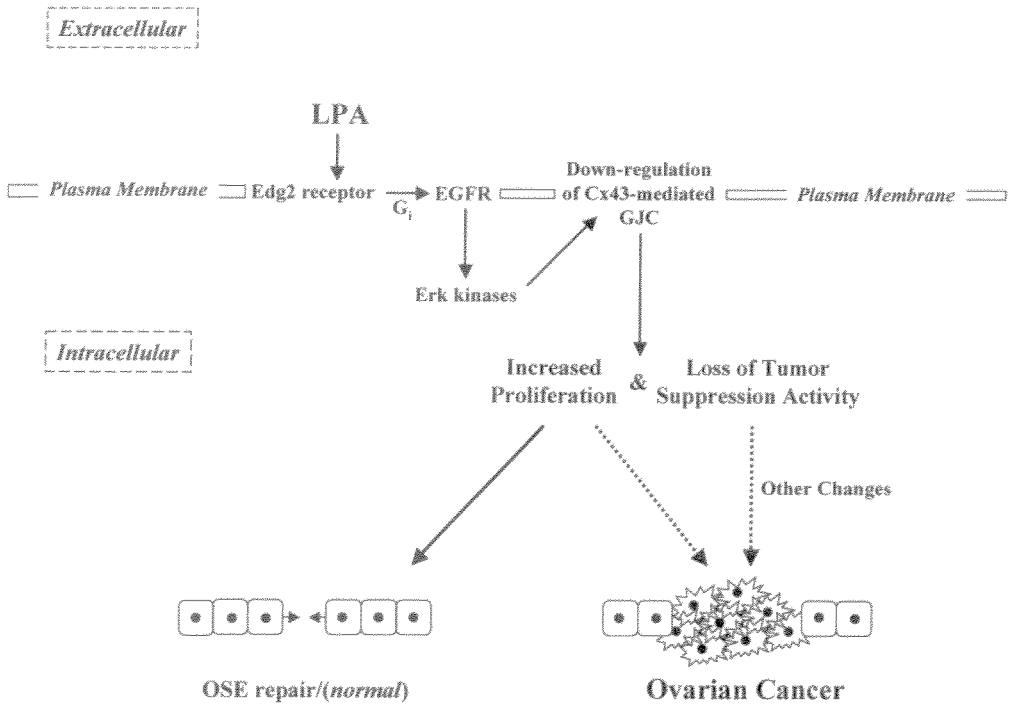

Figure 1.— LPA signaling in normal rat ovarian surface epithelial (ROSE) cells.
LPA initiates signaling by binding to an extracellular site on the Edg2 transmembrane-receptor, leading to the Gi-mediated transactivation of the epidermal growth factor receptor (EGFR), also a transmembrane receptor. Transactivation of the EGFR leads to the activation of Erk kinases, increased phosphorylation of Cx43, and the down-regulation of GJC. The down-regulation of Cx43's growth-suppressive function allows enhanced cell proliferation that aids in wound repair. However, the enhanced cell proliferation may also allow abnormal cells to escape from the normal tumor-suppressor function of Cx43 and thus proliferate and contribute to the development of ovarian cancer.

Connexin Expression In the Ovarian Surface Epithelial Cells

Connexins (Cxs) mediate gap junctional communication (GJC) by forming aqueous channels between neighboring cells and facilitating the passive exchange of small molecules and ions, less than one kilodalton in mass. Cxs are integral plasma membrane proteins with cytoplasmically localized N- and C- terminal domains that create a single intracellular loop. To form a complete intercellular channel, each cell contributes a Cx hexamer, or a half channel, that docks with a hexamer from a neighboring cell.

Since the reduction or loss of GJC and/or Cx expression is associated with enhanced cell proliferation in tumor cells as compared to normal cells[7,8], Cxs are thought to have a tumor suppressor function. Likewise, inducing the expression of Cx43 in tumor cells and in Cx43-null cells decreases rates of cell proliferation[9]. Importantly, forced expression of Cx43 in Cx43-deficient ovarian carcinoma cells increases the cells' dependence on serum growth factors and reduces their tumorigenicity in nude mice[10]. Normal rat OSE (ROSE) cells and normal human OSE (HOSE) cells primarily express the Cx43 protein, whereas Cx43 and GJC are greatly reduced or absent in neoplastic derivatives of ROSE cells and in human ovarian adenocarcinoma cells[11]. These data support the role of the Cx43 gap junction protein, in tumor suppression of OSE cells. However, the precise mechanisms by which Cx43 exerts its anti-proliferative effect are not yet understood.

LPA-Mediated Signaling In Ovarian Surface Epithelial Cells

LPA affects the regulation of cell growth, adhesion, and migration by engaging the Edg2/LPA_1, Edg4/LPA_2, and Edg7/LPA_3 transmembrane receptors present on the surface of normal and transformed ovarian cells[12]. The Edg receptors couple to G proteins (GPCRs, G protein-coupled receptors) comprised of alpha, beta, and gamma subunits that initiate unique signaling pathways. The activation of a particular signaling pathway is determined by the different G-alpha subclasses, either G_s, G_i, G_q, or $G_{12/13}$. The Edg2 receptor primarily signals through a G_i-dependent pathway and the Edg7 receptor through a G_q-dependent pathway while the Edg4 receptor signals through G_i- and G_q- coupled pathways in OSE cells[13].

In some cell types, the transactivation of the epidermal growth factor receptor (EGFR)/Her-1 is required for mediating the LPA-induced activation of extracellular-signal-regulated kinases (Erks)[12]. The EGFR gene is often amplified, over expressed, or mutated in ovarian carcinomas, resulting in various alterations of the EGFR signaling pathways, including ligand-independent EGFR signaling[13]. Historically, poor prognosis has been associated with over expression of the EGFR in ovarian carcinomas, however recent univariate and multivariate analysis has demonstrated a lack of correlation between EGFR over expression and prognosis[14-16]. Alterations in EGFR-mediated signaling pathways have been implicated in human cancer,[17] and antibody therapies directed against the EGFR are the subject of ongoing clinical research[18]. These trials show promise in the treatment of ovarian cancer.

LPA Transiently Down-Regulates Connexin43 Function in Ovarian Surface Epithelial Cells

The EGFR is known to activate Erk kinases, which have been shown to play a key role in the disruption of GJC and the phosphorylation of Cx43[19-21]. However, Postma et al. have suggested that the non-receptor tyrosine kinase, c-Src, and not Erk kinases, are critical for the disruption of GJC induced by LPA in rat fibroblast cells; however, tyrosine phosphorylation of Cx43 was not detected and the precise mechanism for the c-Src-mediated disruption of GJC was not determined[22]. We have demonstrated in normal rat OSE cells that LPA-induced transactivation of the EGFR is required for the transient down-regulation of Cx43-mediated GJC, the activation of Erk5, and the maximal increase in Cx43 phosphorylation (Lin et al., manuscript in revision). These results may support the conclusions of Cameron et al., which suggest that Erk5 is more important than the more studied Erk1 and Erk2 kinases[21] in cells treated with epidermal growth factor.

Conclusions

To better understand the pathogenesis and development of ovarian cancer, studies of the LPA-mediated signaling pathways that are activated in wound repair in response to follicular rupture in normal OSE cells are required. It is thought that Cx-mediated GJC between neighboring cells is important for coordinating the responses of different cell types in wound repair and it has been shown that the down-regulation of Cx43 increases the rate of wound closure and reduces inflammation and scarring in a skin wound-repair model[23]. Although the transient down-regulation of Cx43 by LPA may play an important role in enhancing normal OSE cell proliferation for repair of the ovarian epithelium after follicular rupture, the down-regulation of GJC by LPA may also allow aberrant cells that naturally arise during cell proliferation to escape from the normal growth-suppressive effects of Cx43. This possible course of events could contribute to the development of ovarian cancer. Considering these two possible outcomes resulting from LPA's down-regulation of Cx43 function in OSE cells, LPA may act either as a friend or a foe of the ovarian surface epithelium.

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